



NDA 022545/S-010

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936

Dear Ms. Kneafsey:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 22, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekamlo (aliskiren/amlodipine) 150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg and 300 mg/10 mg Tablets.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. In **HIGHLIGHTS** and **Full Prescribing Information**, the boxed warning was changed:

**WARNING: FETAL TOXICITY**

- **When pregnancy is detected, discontinue Tekamlo as soon as possible (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1)**

2. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

**5.1 Fetal/Neonatal Morbidity and Mortality**

The use of drugs that act directly on the renin-angiotensin-aldosterone system during pregnancy can cause fetal and neonatal morbidity and death. No animal studies were conducted with Tekamlo; however, decreased fetal birth weight was observed in animal studies with aliskiren and intrauterine deaths were observed in animal studies with amlodipine. Tekamlo can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, discontinue Tekamlo as soon as possible. If Tekamlo is

used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

To:

### **5.1 Fetal toxicity** **Pregnancy Category D**

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Tekamlo as soon as possible [*see Use in Specific Populations (8.1)*].

3. Under **USE IN SPECIFIC POPULATIONS**, the section was changed from:

### **8.1 Pregnancy**

Pregnancy Categories C (first trimester) and D (second and third trimesters) [*see Warnings and Precautions (5.1)*].

The use of drugs that act directly on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy can cause fetal and neonatal morbidity and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in retrospective data. No animal studies were conducted with Tekamlo; however, decreased fetal birth weight was observed in animal studies with aliskiren and intrauterine deaths were observed in animal studies with amlodipine. Tekamlo can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, discontinue Tekamlo as soon as possible. If Tekamlo is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

#### **Human Data and Clinical Considerations**

Maternal hypertension is associated with increased risks for preterm delivery, intrauterine growth restriction, placental abruption, preeclampsia, and perinatal mortality. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. Renin inhibitors (like aliskiren), angiotensin II receptor antagonists and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. Based on several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy is associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria,

reversible or irreversible renal failure, and death. Decreased fetal renal function may result in oligohydramnios and associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have been reported in women using these drugs, but it is not clear whether these occurrences were due to drug exposure. Limited data are conflicting about whether first trimester use of ACE inhibitors is associated with an increased risk of birth defects, but the drugs' mechanism of action raises a theoretical concern.

When pregnancy occurs in a patient using Tekamlo, the physician should discontinue Tekamlo treatment as soon as possible. Inform the patient about potential risks to the fetus based on the time of gestational exposure to Tekamlo (first trimester only or later). If exposure occurs beyond the first trimester, perform an ultrasound examination. In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, serial ultrasound examinations should be used to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Tekamlo treatment and about pregnancy management should be made by the patient and her physicians. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants exposed to Tekamlo in-utero should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

To:

## **8.1 Pregnancy**

### **Pregnancy Category D**

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Tekamlo as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Tekamlo, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Tekamlo for hypotension, oliguria, and hyperkalemia. [*see use in Specific Populations (8.4)*]

#### Animal Data

No reproductive toxicity studies have been conducted with the combination of aliskiren and amlodipine besylate. However, these studies have been conducted for aliskiren and amlodipine besylate alone.

#### Aliskiren

In developmental toxicity studies, pregnant rats and rabbits received oral aliskiren hemifumarate during organogenesis at doses up to 20 and 7 times the maximum recommended human dose (MRHD) based on body surface area ( $\text{mg}/\text{m}^2$ ), respectively, in rats and rabbits. (Actual animal doses were up to 600  $\text{mg}/\text{kg}/\text{day}$  in rats and up to 100  $\text{mg}/\text{kg}/\text{day}$  in rabbits.) No teratogenicity was observed; however, fetal birth weight was decreased in rabbits at doses 3.2 times the MRHD based on body surface area ( $\text{mg}/\text{m}^2$ ). Aliskiren was present in placentas, amniotic fluid and fetuses of pregnant rabbits.

#### Amlodipine

In developmental toxicity studies, pregnant rats and rabbits received oral amlodipine maleate during organogenesis at doses approximately 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area ( $\text{mg}/\text{m}^2$ ), respectively, in rats and rabbits. (Actual animal doses were up to 10  $\text{mg}/\text{kg}/\text{day}$ .) No evidence of teratogenicity or other embryofetal toxicity was observed. However, litter size was decreased approximately 50% and the number of intrauterine deaths was increased approximately 5-fold for rats receiving amlodipine maleate at doses approximately 10 times the MRHD based on body surface area ( $\text{mg}/\text{m}^2$ ) for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

4. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, a new section was added:

#### Neonates with a history of in utero exposure to Tekamlo:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. These patients should be asked to report pregnancies to their physicians as soon as possible.

To:

Female patients of childbearing age should be told about the consequences of exposure to Tekamlo during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

6. The revision date and version number were updated.

**The following changes were made to the Patient Information:**

7. Under **What is the most important information I should know about Tekamlo?**, the section was changed from:

**If you become pregnant while taking Tekamlo, stop taking Tekamlo and call your doctor right away. Tekamlo may harm an unborn baby, causing injury or death. Talk to your doctor about other medicines to treat your high blood pressure if you plan to become pregnant.**

To:

**Tekamlo can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking Tekamlo, tell your doctor right away.**

8. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN  
Regulatory Project Manager for Safety  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

MARY R SOUTHWORTH  
02/02/2012